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10/579,032	05/10/2006	Sei Kwang Hahn	HAHN5	3877

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,032	HAHN ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,11,20,22,24-27 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *11,20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8, 24-27 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 28 Oct 2009, in which claims 4, 26 and 31 are amended to correct minor informalities and withdrawn claims 20 and 22 are amended to change dependency.

This application is the national stage entry of PCT/JP04/16948, filed 15 Nov 2004; and claims benefit of foreign priority documents JAPAN 2003-385054, filed 14 Nov 2003; JAPAN 2003-407681, filed 05 Dec 2003; and JAPAN 2004-259157, filed 07 Sep 2004; currently an English language translation of these foreign priority documents have not been filed.

Claims 4-8, 11, 20, 22, 24-27 and 31-36 are pending in the current application. Claims 11, 20 and 22, drawn to non-elected species, are withdrawn. Claims 4-8, 24-27 and 31-36 are examined on the merits herein.

Objections Withdrawn

Applicant's Amendment, filed 28 Oct 2009, with respect to objections to claims 26 over the apparent misspelling of drug has been fully considered and is persuasive, as amended claim 26 corrects this minor informality.

This objection has been **withdrawn**.

Rejections Withdrawn

The previously recited rejection of claim 23 rejected under 35 USC 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (US Patent Application Publication 2003/0211166, published 13 Nov 2003, of record) in view of Schense et al. (US Patent Application Publication 2003/0012818, 16 Jan 2003, of record) and further in view of Shu et al. (Biomacromolecules, 2002, 3, p1304-1311, of record) was due to a typographical error, as the status of claim 23 is (Canceled).

This rejection of claim 23 has been **withdrawn**.

Election/Restrictions

Claims 11, 20 and 22 remain withdrawn as being drawn to non-elected species. MPEP 809 provides that when all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked inventions must be withdrawn, and any claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability. Upon finding of allowable genus claims the species will be rejoined.

The following grounds of rejection are reiterated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended Claims 4-8, 24-27 and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (US Patent Application Publication 2003/0211166, published 13 Nov 2003, of record) in view of Schense et al. (US Patent Application Publication 2003/0012818, 16 Jan 2003, of record) and further in view of Shu et al. (Biomacromolecules, 2002, 3, p1304-1311, of record).

Yamamoto et al. teaches microspheres of hyaluronic acid to deliver a drug or active substance (page 2, paragraphs 27 and 28). Yamamoto et al. teaches the microspheres prepared by standard spray drying techniques, in which a solution containing the hyaluronate polymer is dispersed to form atomized, or microparticulate, droplets which condense and dry, concentrating the solution (page 2, paragraph 29). Yamamoto et al. teaches chemical cross-linking of the microspheres co-formulated into the microspheres, added to the starting hyaluronic acid starting material or after fabrication in the partially hydrated state (page 2, paragraph 30). Yamamoto et al.

teaches using a starting solution containing 0.5% concentration HA, a dilute solution (page 3, paragraph 37). Yamamoto et al. teaches the method wherein said dilute solution contains the crosslinking agent prior to dispersing the solution by spraying (page 4, paragraphs 43 and 44). Yamamoto et al. teaches the process wherein the microspheres made have a diameter between 0.01 and 100 microns (page 2, paragraph 28). Yamamoto et al. teaches the process wherein the microspheres are capable of providing a sustained drug delivery effect (page 3, paragraph 36). Yamamoto et al. teaches drugs or other active agents encapsulated in the microsphere to provide local drug delivery (page 3, paragraph 35). Yamamoto et al. teaches the microspheres are crosslinked to increase biodegradation time in-situ (page 2, paragraph 28), and one of skill in the art would readily understand biodegradation to involve enzymatic degradation. Yamamoto et al. teaches microspheres so made are injectable (page 4, examples 4 and 5 at right column).

Yamamoto et al. does not teach the specific method wherein the polysaccharide comprises at least one unit represented by Formula I or at least one unit represented by Formula II or the specific crosslinking reaction is a reaction in which crosslinkages are formed by addition reaction between a mercapto group and an unsaturated C-C bond (instant claim 31). Yamamoto et al. does not teach the specific method wherein the dilute solution before the crosslinking reaction contains a drug, and the drug is held in the microparticles obtained after the crosslinking reaction (instant claims 7, 26 and 30). Yamamoto et al. does not teach the specific method wherein the crosslinking reaction does not cause drug denaturation even in the presence of the drug (instant claims 8 and

27). Yamamoto et al. does not teach the specific method wherein the drug is a protein (instant claim 33). Yamamoto et al. does not teach the specific method wherein the sustained release period of the carrier is 24 hours or more (instant claim 34), which is interpreted as an intended use of the product made by the instantly claimed method of making. Yamamoto et al. does not teach the specific method wherein the sustained release period of the carrier is 5 days or more (instant claim 35), which is interpreted as an intended use of the product made by the instantly claimed method of making.

Schense et al. teaches bioactive molecules entrapped within a matrix for the controlled delivery of said bioactive molecules wherein said bioactive molecules are entrapped during gelation of the matrix (page 1, paragraph 12). Schense et al. teaches the bioactive molecules include proteins such as growth factors, peptides and enzymes (page 4, paragraph 54). Schense et al. teaches the matrix formed by the reaction of a multi-thiol, or mercapto groups, and a conjugated unsaturated group in a solution that contains a bioactive molecule, or drug, mixed together to perform the crosslinking reaction (page 6, paragraphs 81 and 82). Schense et al. defines a conjugated unsaturated group to include carbon-carbon bonds (paragraph 25 spanning pages 2 and 3), and a conjugated group necessarily has two or more carbon-carbon double bonds in conjugation. Schense et al. teaches the matrix-forming reaction is self-selective, meaning the thiol preferentially reacts with the conjugated unsaturated group rather than other biological compounds such as the bioactive molecule, indicating that the matrix-forming reaction does not cause drug denaturation (page 3, paragraphs 26 and 27). Schense et al. does not explicitly describe the gelation or matrix-forming

reaction as a crosslinking reaction, however one of ordinary skill in the art would understand the terms gelation and matrix as described in page 3 paragraphs 29 and 30 to refer to the formation of a crosslinked polymer. Schense et al. teaches the matrix made of natural polymers such as hyaluronic acid (page 3, paragraph 39). Schense et al. teaches a matrix wherein the bioactive molecule is released completely within several weeks (page 7, paragraph 85), teaching that the product is capable of being used in an intended use such that the sustained release period of the carrier is 5 days or more.

Yamamoto et al. in view of Schense et al. does not specifically teach the specific method wherein the polysaccharide comprises at least one unit represented by Formula I or at least one unit represented by Formula II.

Shu et al. teaches thiol-modified hyaluronic acids used in crosslinking to slow down degradation are known for the purpose of in the field of drug delivery (page 1304, abstract, left column paragraph 2 and right column paragraph 1). Shu et al. teaches a thiol-modified hyaluronic acids having the structure having a thiol reading upon instant Formula I (page 1306, figure 2 at top of page).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Yamamoto et al. in view of Schense et al. and further in view of Shu et al. All of Yamamoto et al., Schense et al. and Shu et al. are drawn to crosslinked hyaluronic acid for sustained release of a bioactive molecule. One of ordinary skill in the art at the time of the invention would be motivated to combine the invention of Yamamoto et al. in view of Schense et al. to improve a similar product and

process in the same way because Schense et al. teaches the improvement increases the retainable concentration of bioactive molecules in a matrix (Schense et al. page 1, paragraph 9). It would have been obvious to substituted the thiol-modified hyaluronic acids taught by Shu et al. for the thiol-modified hyaluronic acids taught by Schense et al. because both thiol-modified hyaluronic acids are known for the same purpose of forming crosslinked hyaluronic acids to slow down degradation in the field of drug delivery.

Response to Applicant's Remarks:

Applicant's Remarks, filed 28 Oct 2009, with regard to Yamamoto et al. in view of Schense et al. and further in view of Shu et al. have been carefully and fully considered and not found to be persuasive.

Applicant notes that Yamamoto et al. at page 4, paragraph 43 teaches the method wherein said dilute solution contains the hyaluronic acid (HA) and crosslinking agent prior to dispersing the solution by spraying are allowed to react for 24 hours to undergo crosslinking. Applicant emphasizes that in the instant invention the crosslinking reaction occurs in the microparticulate droplets produced by spraying of the reaction solution. In acknowledgement of Applicant's description of what is asserted to be a key technical feature of the claimed method, the instant specification at paragraph 20 spanning pages 10-11 describes embodiments of the method wherein the crosslinking is performed during concentration or in parallel with drying, and at page 20, paragraph 56 wherein the method is performed so as to crosslink the hyaluronic acid during concentration and drying. However, this limitation is not found within the claims

and it is improper to construe the claims by importing such limitations from the specification into the claims, see MPEP 2111.01 II. The instant invention as recited in the claims requires in claim 31 that the concentrating of the solution in step c) facilitates a crosslinking addition reaction, but it does not exclude the method wherein the crosslinking reaction is allowed to react for 24 hours prior to dispering the solution according to step b). It would have been obvious to one of ordinary skill in the art that the spraying taught at Yamamoto et al. at page 4, paragraphs 44 would concentrate the solution and therefore facilitate any remaining crosslinking addition reaction, based on the understanding of concentration-dependent reaction mechanism possessed by one of ordinary skill in the art. Therefore the instant invention as recited in the claims encompasses the process made obvious by Yamamoto et al. in view of Schense et al. and further in view of Shu et al.

Applicant takes the position that Schense et al. teaches away from the instant invention and from combination with Yamamoto et al. and Shu et al. because Schense et al. teaches at page 6, paragraph 75 that "[d]epending on the precursor components and their concentration, gelling can occur quasi-instantaneously after mixing", giving a gelled material that is difficult to inject and therefore not suitable for administration by way of injection according to instant claim 32. However, Yamamoto et al. is drawn to low concentration formulation of microspheres that have utility when injected (Yamamoto et al. abstract). The teaching of Schense et al. taken as a whole can be interpreted as establishing that one of ordinary skill in the art recognizes that the gelling depends on the precursor components and their concentration. It is the combination of

Yamamoto et al. in view of Schense et al. and further in view of Shu et al., with Yamamoto et al. teaching the precursor components and their concentration that give microspheres that have utility when injected and Schense et al. establishing that one of ordinary skill in the art recognizes that the gelling depends on the precursor components and their concentration, that renders the instant method obvious. While Schense et al. must be considered as a whole, including disclosures that teach away from the claim, it is found that the teaching of Schense et al. as interpreted above does not teach away from the invention made obvious by the combination of Yamamoto et al. in view of Schense et al. and further in view of Shu et al.

Applicant notes that Schense et al. and Shu et al. do not disclose the materials to form microparticles. Applicant raises questions the reasonable expectation of success to combine Yamamoto et al. in view of Schense et al. and further in view of Shu et al. MPEP 2143.02 II. provides "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." Shu et al. teaches that it is known to one of ordinary skill in the art that a variety of hydrophobic modifications and chemical cross-linking strategies have been explored with regard to medical HA materials in order to improve the biomechanical properties and make materials that are more mechanically and chemically robust (Shu et al. page 1304, paragraph spanning bottom of left column and top of right column). Shu et al. teaches the disulfide cross-linking method was developed for the preparation of HA hydrogel films (Shu et al. page 1310, right column,

Conclusions). Yamamoto et al. teaches the microsphere formulations of HA having medical utility due to mechanical and chemical properties of flowability, physical stability and degradability (Yamamoto et al. abstract). Yamamoto et al. describes this in terms of film forming properties (Yamamoto et al. page 4, paragraph 43). Based on the teaching of Shu et al. with regard the knowledge of one of ordinary skill in the art about the variety of hydrophobic modifications and chemical cross-linking strategies explored with regard to medical HA materials to improve the biomechanical properties and the teaching of Yamamoto et al., it is found that the art supports at least some degree of predictability providing a reasonable expectation of success in combining Yamamoto et al. in view of Schense et al. and further in view of Shu et al., absent a showing of evidence that there was no reasonable expectation of success.

This rejection is maintained and made FINAL.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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